

44. (New) The method of claim 25, wherein the chemokine is SLC.
45. (New) The method of claim 25, wherein the chemokine is TECK.
46. (New) The method of claim 25, wherein the chemokine is BLC.
47. (New) The method of claim 25, wherein the chemokine is CTACK.
48. (New) The method of claim 25, wherein the chemokine is mMIP-1 $\gamma$ .
49. (New) The method of claim 25, wherein the chemokine is vMIPII.

REMARKS

I. Interview

The undersigned thanks Examiner Bridget Bunner and Examiner Elizabeth Kemmerer for their courtesy in discussing this case with the undersigned on November 19, 2002.

II. Status of Claims

Claims 1-25 and 27-36 are pending, with claim 26 previously canceled and claims 1-24 and 28-36 withdrawn as being directed to non-elected inventions. Upon entry of this amendment, claims 25 and 26 are amended without prejudice or disclaimer and new claims 37-49 added.

The amended and new claims find support throughout the specification including, for example, the following sections of the specification:

<u>Claim</u>	<u>Support</u>
25 and 26	pages 16-19
37	page 3, lines 31-32
38 and 40	page 35, line 20
39	page 34, lines 23-24
41	page 35, lines 16-17 and 32-33

42	page 40, lines 24 to page 46, line 23; and original claim 28
43-49	page 57, lines 9-17; FIGS. 4A and 4B; original claim 26.

### III. Amendment to Specification

The cross-reference section has been amended to indicate that this application is a divisional application of U.S. 09/686,020, filed October 10, 2000. This is appropriate because the current claims correspond to claims from one of the restriction groups in the parent application. The specification has also been amended to move the Field of Invention section so it comes after the Cross-References to Related Application section. The amendment to the specification at page 53 is supported, for example, at page 55, lines 19-21. The other changes are to remove the hyperlinks as requested by the Examiner. None of these amendments add new matter.

### IV. Elections/Restrictions

Applicants' traverse of the restriction requirement between Groups VII and VIII is maintained. As acknowledged in the current Office Action, the method described in claim 28 involves all the steps recited in claim 25 plus an additional step (page 3). In view of the comprising language in claim 25, claim 25 can encompass an additional formulation step as recited in claim 28. So as pointed out in the previous response, in conducting a search of the claims in Group VII, the Examiner will necessarily have to conduct a search of the method as recited in claim 28. Applicants also note that in the restriction requirement issued in the parent of this application, the current Examiner included claim 28 within the same restriction group as claim 25, presumably for the foregoing reason. In view of these reasons, Applicants request that the Examiner reconsider this particular restriction requirement and rejoin claim 28 into the instant application.

Applicants also note that the Examiner has limited examination to mMIP-1 $\gamma$ , the elected chemokine species. Limiting examination to this particular species rather than examining the full breadth of the claim with respect to the other chemokines recited in claim 25 is in error. MPEP 803.02 emphasizes that in Markush type claims, such as claim 25, that examination must continue with respect to all species, unless prior art is identified that anticipates the claim or renders it obvious, as indicated in the following section:

If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. . . .

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. MPEP 803.02 (emphasis added).

In the current Office Action, none of the claims are rejected as anticipated or obvious over the prior art. So all the chemokine species recited in claim 25, not just the elected species, must be examined on the merits, unless prior art that anticipates or renders the claim obvious is identified. Applicants thus request that the claims be examined in accordance with MPEP 803.02 prior to issuance of the next Office Action.

V. Drawings

A set of formal drawings are enclosed with this response.

VI. Objections to the Specification

The specification is objected to for inclusion of hyperlinks. Applicants have deleted these.

The title of the application is objected to as not clearly indicating the subject matter of the application. Applicants are appreciative of the Examiner's suggested title and have amended the title accordingly.

VII. Claim Objections

Claim 25 is objected to as including non-elected species of chemokines. For the reasons set forth above in the section addressing the restriction and species election requirement, Applicants submit that the additional species need not be excluded from the claim absent the Office identifying prior art that anticipates the claim or renders it obvious.

VIII. Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 25 and 27 are rejected as allegedly not being enabled for three reasons: 1) one of ordinary skill in the art would purportedly find it difficult to identify an appropriate form of CCX CKR to utilize in the methods, 2) the specification allegedly lacks sufficient guidance regarding the type of test compounds to screen, and 3) one of ordinary skill in the art allegedly cannot determine whether CCX CKR polypeptide can bind mMIP-1 $\gamma$  chemokine. In view of these alleged shortcomings, the Office Action concludes that it would take undue experimentation to practice the currently claimed invention. Applicants respectfully disagree for the following reasons.

A. Selection of an Appropriate CCX CKR Protein for use in Screening is Enabled

As the Office Action notes, there are a number of factors to consider when making a determination of whether undue experimentation is required to practice invention, such as breadth of the claims, the direction and guidance in the specification, and the existence of working examples (see MPEP 2164.01(a)). A consideration of these factors demonstrates that the present claims are enabled.

Applicants initially note that claim 25 has been amended to clarify that the CCX CKR polypeptide utilized in the screening methods has the amino acid sequence as set forth in SEQ ID NO:2, or is a fragment or variant thereof. Further, the claim requires that the CCX CKR polypeptide, fragment or variant binds at least one of the following chemokines: ELC, SLC, TECK, BLC, CTACK, mMIP-1 $\gamma$  or vMIPII. While this was implicit in the original wording of the claim, this feature is made explicit in the claims as amended. Thus, the form of CCX CKR

utilized in the current claims is specifically defined both in terms of amino acid sequence *and* with respect to binding activity.

With respect to the extent of disclosure in the specification, it provides extensive teachings regarding the specific sequence of the full-length CCX CKR polypeptide (SEQ ID NO:2) and guidance regarding appropriate substitutions to obtain variants (see, e.g., page 7, line 29 to page 8, line 5; and page 16, line 22 to page 19, line 10). And the application discloses details concerning how to screen polypeptides to determine if they are suitable for use in the current methods, e.g., if they can bind one or more of the chemokines recited in the claim (see, e.g., the screening method described in Examples 4 and 5 on pages 55 –56 that were utilized to interrogate the ability of nearly 80 different chemokines to bind CCX CKR).

The application also includes a working example that describes in detail how to make and use a CCX CKR polypeptide, fragment or variant to conduct screening methods such as currently claimed. Example 3 for instance sets forth methods for preparing a fusion protein (a FLAG epitope-tagged CCX CKR polypeptide) for use in screening. Example 7 describes the use of the fusion protein to screen a library of small molecules for activity as an inhibitor or enhancer of chemokine binding. Specific chemical structures for compounds identified by this method as having such activity are shown in Table 1 on page 38.

Thus, it is submitted that in view of the fact that CCX CKR is defined in claim 25 in both chemical and functional terms, the extensive discussion of the forms of CCX CKR that can be utilized in the specification, and the working examples, that one of ordinary skill in the art would have been able to identify appropriate polypeptides, fragments or variants for use in the currently claimed screening methods. This is especially true, given that the application also sets forth detailed methods for identifying proteins that have the requisite functional activity as required in claim 25.

Although it is believed the foregoing reason adequately address the enablement issue with regard to this aspect of the present invention, Applicants turn to address the specific shortcomings that are purported to exist. The Office Action states that “the skilled artisan cannot determine which specific CCX CKR polypeptide sequence is used in the working examples of

the instant application since the definition of CCX CKR in the specification encompasses variants and fragments of full-length CCX CKR.”

In response, Applicants direct the Examiner’s attention to several sections in the Example section of the specification. In the introductory section in which the materials utilized to conduct the experiments are listed, it is explained that a Flag epitope tagged form of CCX CKR (i.e., a fusion protein) was utilized to conduct the experiments described in the Examples (page 53, lines 23-26). This point is reiterated in Example 1 (see, page 54, lines 20-22). Additional details regarding the preparation of the fusion protein are set forth in Example 3. In fact, Example 3 explicitly states that “[t]o assess the functional properties of the protein encoded by CCX CKR cDNA, *including its potential chemokine binding profile*, we constructed expression plasmids encoding CCX CKR with an N-terminal Flag epitope.” (emphasis added). Thus, the binding studies described in Examples 4-6 were conducted with this fusion protein. This point is emphasized in Examples 7 and 8 (see, page 58, lines 24-25 and page 59, line 11). So, in fact, the specification clearly defines for the skilled artisan the form of CCX CKR that was utilized in the working examples.

**B. Application Provides Identity of Exemplary Modulators**

The second major contention in the Office Action concerns the amount of disclosure required with respect to the type of compounds that could be screened and the identity of compounds having modulatory activity. Specifically, the Office Action first contends that the specification does not disclose the identity of any modulator of CCX CKR to a chemokine and that one skilled in the art cannot predict the structure or identity of the compounds identified by the claimed screening methods. It is further asserted that the specification lacks guidance concerning the type of compounds that should be screened. The absence of such teaching is said to force the skilled artisan to resort to trial and error in determining which compounds might yield the desired activity. This alleged paucity of information is said to require undue experimentation to practice the invention.

Applicants initially note that the “invention that one skilled in the art must be enabled to make and use is that defined by the claims(s) of the particular application or patent” (MPEP 2164; emphasis added). The details the Examiner requires are not necessary to practice the currently claimed invention. For example, the identity of specific modulators that can be detected by the current screening methods are not required to practice the method. While the identity of such modulators may be necessary to enable a claim directed to modulators per se, one can conduct the current methods without knowing in advance the identity of active modulators. In fact, the very goal of a screening method is to identify as yet unknown active modulators.

While it is submitted that identification of specific modulators is unnecessary to enable the present screening claims, Applicants direct the Examiner’s attention to Table I on page 38 that provides specific chemical structures of two antagonists and one agonist. So contrary to the assertion in the Office Action, one of ordinary skill in the art can use these exemplary modulators as the basis for identifying further modulators.

With respect to the alleged need for the specification to describe the types of compounds that could be screened, Applicants submit that this level of specificity is not required to practice the currently claimed invention. To a large extent and by definition, the value of screening methods lie in their ability to be used to rapidly identify active compounds from large pools of diverse compounds.

The position taken in the Office Action suggests that the Examiner considers a discussion of the type of compounds likely to show activity necessary to minimize the screening of compounds that turn out to lack activity. This concern is unwarranted. Because the goal in a screening method is to determine whether or not a given compound has a desired activity, that a negative result is obtained for a compound does not mean that the screening method is inoperative. Indeed, it is quite typical to perform a screening method in which the vast majority of compounds give negative results. And negative results are nonetheless useful in excluding potential test compounds and providing guidance regarding the type of compounds unlikely to exhibit activity.

Although Applicants contend that details regarding the class of compounds that might be useful in the screening methods is not required, it is nonetheless noted that the specification provides considerable information on this very issue. The specification for instance demonstrates that CCX CKR is a chemokine receptor (see, e.g., page 2, line 14). With this knowledge alone, those skilled in the art could narrow the field of potential test compounds to a subset of compounds likely to show activity (e.g., compounds with structures that mimic known chemokines). Additionally, the specification identifies specific chemokine ligands that bind to CCX CKR (e.g., ELC, SLC, TECK, BLC, CTACK, mMIP-1 $\gamma$  or vMIPII; see, e.g., page 57, lines 11-17; and FIGS. 4A and 4B). Those of ordinary skill would immediately recognize that useful inhibitors, for example, would be mimetics of these specific chemokines. And the Applicants have screened nearly 80 different chemokines to identify those that bind CCX CKR and those that do not, thus providing an extensive profile or fingerprint regarding CCX CKR binding (Example 5, page 57). The binding studies were continued beyond a determination of qualitative binding to ascertain quantitative binding affinities (see, e.g., Example 6 and FIG. 4B). With this wealth of binding information, one of ordinary skill would be well positioned to identify structural features important in binding, as well as features that impede binding. And to reiterate, the specification also discloses specific chemical structures of two antagonists and one agonist. The structure of these compounds would further inform one of ordinary skill with respect to the type of compounds that might be particularly valuable in screening.

To summarize, even if one assumes that the specification must include a description of the type of compounds to be screened, one of ordinary skill in the art, having the current specification in hand, would not have to resort “to trial and error” to identify suitable test compounds. To the contrary, the extensive binding studies described in the specification would enable the ordinary practitioner to make highly educated predictions of additional suitable compounds.

C. Application Enables Screening Methods with mMIP-1 $\gamma$



The final assertion in the Office Action with respect to enablement is that there are no working examples describing methods in which CCX CKR is contacted with a test agent in the presence of mMIP-1 $\gamma$ , the elected chemokine species. Applicants reject the implication that an example of a screening method specifically conducted with mMIP-1 $\gamma$  is required to enable the current screening methods in view of the detailed guidance regarding how to conduct the screening methods. The specification, for instance, includes a detailed description of how to conduct screening methods (see, e.g., pages 33-38); a specific example of how to conduct such screening methods is also included (see, Example 7). Disclosure such as this is more than adequate to enable one of ordinary skill to practice the present screening methods without undue experimentation.

Nonetheless, the application provides an example describing a competitive binding experiment in which CCX CKR was contacted with mMIP-1 $\gamma$  in the presence of the labeled chemokines ELC or TECK. This example is directly applicable to the information the Examiner seeks.

The Office Action also contends that “one skilled in the art cannot predict that the CCX CKR polypeptide is capable of binding mMIP-1 $\gamma$ .” It is not clear what is meant by this statement. If the Examiner is saying that there is no evidence in the application that mMIP-1 $\gamma$  can even bind CCX CKR, then Applicants direct the Examiner’s attention to Examples 5 and 6 (pages 57-58) which describe the experiments which demonstrated that CCX CKR binds mMIP-1 $\gamma$  (see, specifically page 57, line 13; see also FIGS. 4A and 4B which provide relative and specific binding affinities for mMIP-1 $\gamma$  to CCK CKR).

If instead the Examiner is asserting that it is unclear what forms of CCX CKR might bind mMIP-1 $\gamma$ , this has been dealt with above in section A.

Because the specification fully enables the currently claimed methods for the reasons set forth above, it is requested that the rejection of the claims for lack of enablement be withdrawn.

IX. Claim Rejection under 35 U.S.C. §112, Second Paragraph

Claims 25 and 27 are rejected for inclusion of acronyms used for the chemokines listed in these claims. The full names of the chemokines have been added to claim 25 to overcome this rejection.

Claim 25 is also rejected for allegedly lacking appropriate antecedent basis. The claim has been amended as suggested by the Examiner.

X. Information Disclosure Statement

A checked version of the Information Disclosure Statement filed on July 18, 2002 was not provided with the Office Action. If the Examiner has not already done so, it is requested that this IDS be considered and a checked version provided with the next communication.

XI. Marked Up Version

Appendix A entitled "Version with Markings to Show Changes Made" which is attached hereto shows the amendments to the specification, abstract and claims. Appendix B entitled "Pending Claims" provides a list of all the claims as pending following entry of this amendment.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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**APPENDIX A**

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

The title on page 1 has been canceled and replaced with a new title as shown:

**~~CHEMOKINE RECEPTOR~~**

**METHOD FOR IDENTIFYING A MODULATOR OF THE BINDING OF  
CCX CKR POLYPEPTIDE TO A CHEMOKINE**

The paragraph under the heading entitled "Cross-References to Related Applications" on page 1, line 11 has been amended as follows:

This application is a ~~continuation~~ divisional of U.S. Patent Application No. 09/686,020, filed October 10, 2000, which claims benefit of U.S. Provisional Patent Application 60/159,015, filed October 12, 1999, and U.S. Provisional Patent Application 60/159,210, filed October 13, 1999, and U.S. Provisional Patent Application 60/172,979, filed December 20, 1999, and U.S. Provisional Patent Application 60/173,388, filed December 28, 1999, and U.S. Provisional Patent Application 60/186,626, filed March 3, 2000. The disclosure of each of the aforementioned applications is expressly incorporated herein by reference in its entirety and for all purposes.

The paragraph beginning at page 13, line 27 has been amended as follows:

One example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., J. Mol. Biol. 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (~~http://www.ncbi.nlm.nih.gov/~~). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the

neighborhood word score threshold (Altschul et al, supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

The paragraph beginning at page 51, line 15 has been amended as follows:

Chemokines are well known in the art. Exemplary chemokines include those listed in Fig. 4(a) and homologs in other species (e.g., mammalian, mouse, rat rabbit, human, non-human primate, and the like. The following references describe certain cytokines. Additional references describing these and other chemokines known in the art are provided in the R&D Systems Catalog (1999) and (2000) R&D Systems Inc., 614 McKinley Place N.E. MN 55413, the R&D online catalog at [www.rndsystems.com](http://www.rndsystems.com) (e.g., October 10, 1999), both of which are incorporated by reference for all purposes, the CFB (Cytokine Facts Book, 1994, Academic Press Ltd.), Chemokine Facts Book, 1997, Academic Press Ltd., incorporated by reference for all purposes, and the GenBank protein sequence database ~~<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>~~.

The paragraph beginning at page 53, line 21 has been amended as follows:

Human, viral and murine recombinant chemokines were obtained from R&D Systems (Minneapolis, MN; ~~[http://cytokine.rndsystems.com/cyt\\_cat/cyt\\_cat.html](http://cytokine.rndsystems.com/cyt_cat/cyt_cat.html)~~). <sup>125</sup>I-labeled ELC and TECK were obtained from Amersham. Full length CCX CKR expression constructs were made

in pIRESpuro expression vector (Clontech, Palo Alto, CA) with a an N-terminal FLAG epitope tag and prolactin signal sequence, and used to generated stable transfectants in HEK293 cells. Transient and stable transfections for CCX CKR and stalkokines were done using Superfect reagent (Qiagen, Valencia, CA) following manufacturer's protocol. Stables were generated by selecting in 2ug/mL puromycin for 7 days, and expression was confirmed by FACS analysis of the FLAG epitope using anti-FLAG M1 (Sigma, St. Louis, MO) and 2' anti-mouse PE conjugate (Coulter Immunotech, Miami, FL).

IN THE ABSTRACT:

The title on page 65, line 2 has been deleted and replaced with a new title as shown:

~~CHEMOKINE RECEPTOR~~

METHOD FOR IDENTIFYING A MODULATOR OF THE BINDING OF  
CCX CKR POLYPEPTIDE TO A CHEMOKINE

IN THE CLAIMS:

The following claims have been amended as shown without prejudice or disclaimer.

25. (Twice Amended) A method for identifying a modulator of the binding of CCX CKR polypeptide to a chemokine comprising

(a) contacting an isolated or recombinant CCX CKR polypeptide having the amino acid sequence as set forth in SEQ ID NO:2, or a fragment or variant thereof, and the chemokine in the presence of a test compound, and

(b) comparing the level of binding of the chemokine and the polypeptide in (a) with the level of binding in the absence of the test compound, wherein

the CCX CKR polypeptide, fragment or variant can bind the chemokine in the absence of test compound,

the chemokine is selected from the group consisting of ELC (EBI-1-ligand chemokine), SLC (secondary lymphoid organ chemokine), TECK (thymus expressed chemokine), BLC (B-lymphocyte chemoattractant), CTACK (cutaneous T cell attracting chemokine), mMIP-1 $\gamma$

(murine macrophage inflammatory protein 1 $\gamma$ ) and vMIPII (viral macrophage inflammatory protein II), and

a decrease in binding indicates that the test compound is an inhibitor of binding and an increase in binding indicates that the test compound is an enhancer of binding.

27. (Amended) The method of claim 25, wherein said contacting ~~said polypeptide~~ comprises contacting a cell expressing the polypeptide, fragment or variant.

**APPENDIX B**

**PENDING CLAIMS**

1-24. Withdrawn as drawn to non-elected invention.

25. (Twice Amended) A method for identifying a modulator of the binding of CCX CKR polypeptide to a chemokine comprising

(a) contacting an isolated or recombinant CCX CKR polypeptide having the amino acid sequence as set forth in SEQ ID NO:2, or a fragment or variant thereof, and the chemokine in the presence of a test compound, and

(b) comparing the level of binding of the chemokine and the polypeptide in (a) with the level of binding in the absence of the test compound, wherein

the CCX CKR polypeptide, fragment or variant can bind the chemokine in the absence of test compound,

the chemokine is selected from the group consisting of ELC (EBI-1-ligand chemokine), SLC (secondary lymphoid organ chemokine), TECK (thymus expressed chemokine), BLC (B-lymphocyte chemoattractant), CTACK (cutaneous T cell attracting chemokine), mMIP-1 $\gamma$  (murine macrophage inflammatory protein 1  $\gamma$ ) and vMIPII (viral macrophage inflammatory protein II), and

a decrease in binding indicates that the test compound is an inhibitor of binding and an increase in binding indicates that the test compound is an enhancer of binding.

26. Canceled.

27. (Amended) The method of claim 25, wherein said contacting comprises contacting a cell expressing the polypeptide, fragment or variant.

28-36. Withdrawn as drawn to non-elected invention.

37. (New) The method of claim 25, wherein the chemokine is labeled.

38. (New) The method of claim 37, wherein the label is selected from the group consisting of a fluorophore, a chemiluminescent agent, an isotope label, and an enzyme or a combination thereof.

39. (New) The method of claim 25, wherein the test compound is labeled.

40. (New) The method of claim 39, wherein the label is selected from the group consisting of a fluorophore, a chemiluminescent agent, an isotope label, and an enzyme or a combination thereof.

41. (New) The method of claim 25, wherein the CCX CKR polypeptide, fragment or variant is part of a cell fraction.

42. (New) The method of claim 25, further comprising formulating a modulator identified by the method as a pharmaceutical composition.

43. (New) The method of claim 25, wherein the chemokine is ELC.

44. (New) The method of claim 25, wherein the chemokine is SLC.

45. (New) The method of claim 25, wherein the chemokine is TECK.

46. (New) The method of claim 25, wherein the chemokine is BLC.

47. (New) The method of claim 25, wherein the chemokine is CTACK.

48. (New) The method of claim 25, wherein the chemokine is mMIP-1 $\gamma$ .

49. (New) The method of claim 25, wherein the chemokine is vMIPII.